American Journal of Epidemiology
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Vol. 155, No. 2
Printed in U.S.A.

Genetic Contribution to Rate of Change in Functional Abilities among Danish Twins Aged 75 Years or More

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In a previous cross-sectional study of twins, the authors found evidence of a substantial genetic influence on functional abilities among elderly women. It has been suggested that rate of change in functional abilities over time could underlie such findings and that rate-of-change phenotypes may have an even larger genetic component than "level" phenotypes (e.g., functional abilities per se). If so, rate-of-change phenotypes could be more powerful than level phenotypes in studies aimed at identifying specific polymorphisms of importance for aging. In 1995, the authors assessed a population-based sample of 2,401 Danish twins aged 75 years or more. The survivors were recontacted after 2 years and again after 4 years. Consistent mean-level declines, high within-person correlations over time, and substantial heritability in the female sample were observed for functional abilities. Nonetheless, structural-equation analyses revealed only a very modest and nonsignificant heritability for rate of change in functional abilities: 16% (95% confidence interval: 0, 35) for women and 9% (95% confidence interval: 0, 44) for men. This study had a large initial sample size, high participation rates, and a valid and reliable measure of rate of change in a phenotype that had previously shown substantial heritability in cross-sectional analyses in the same twin population. Still, the present study revealed only a modest and nonsignificant genetic influence on rate of change, which suggests that detection of polymorphisms influencing rate of change in functional abilities among the elderly may prove to be difficult. *Am J Epidemiol* 2002;155: 132–9.

activities of daily living; aging; genetics; twin studies; twins; variation (genetics)

Animal models using nematodes, *Drosophila* flies, and mice have clearly demonstrated that single genes can have a substantial influence on aging and life-span (1–3). In humans, premature aging syndromes such as Werner's syndrome also show how mutations in single genes can affect aging and survival (4). Such mutations are rare, but the apolipoprotein E polymorphism provides evidence for more common genetic variants which influence cognitive abilities, disease occurrence, and survival at older ages (5).

The apolipoprotein E polymorphism is the only common polymorphism known to influence the aging process in humans. However, previous studies (including studies of twins) have suggested that in contemporary populations in the industrial world, approximately one quarter of the variation in life-span can be attributed to genetic factors (6–8). There is evidence that cognitive and functional abilities have an even larger genetic component: A Swedish twin study showed that approximately half of the variation in cognitive abilities among persons aged ≥80 years was due to genetic factors (9), and a recent Danish twin study showed that one third to one half of the variation in functional abilities among women aged ≥80 years could be attributed to genetic variation (10).

Both of these studies were cross-sectional, and it has been suggested that rate-of-change patterns underlie such observations—i.e., that genetic factors influence capabilities more through the rate of decline than through the "starting value" or "level value" (11). If this is the case, rate of change may be a more heritable and therefore more powerful phenotype than level phenotypes for research aimed at identifying genes that influence aging processes. However, at present, few data on the genetic contribution to rate-of-change phenotypes are available, and the data have generally shown lower heritability of rate of change than of the phenotypes in cross-sectional analyses (12–15).

In the present study, we sought to estimate the genetic contribution to rate of change in functional abilities among the elderly by using data from the Longitudinal Study of Aging Danish Twins (LSADT). The LSADT started out with assessment of 2,401 Danish twins aged ≥75 years in 1995. The survivors were revisited after 2 years and again after 4 years. A total of 984 individuals, including 127 twin pairs, participated in all three ability assessments.

Received for publication March 7, 2001, and accepted for publication July 19, 2001.

Abbreviation: LSADT, Longitudinal Study of Aging Danish Twins.

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MATERIALS AND METHODS

Study population

The LSADT has previously been described in detail (10, 16–21). In brief, the first wave of the LSADT (LSADT-95) comprised Danish twins who were aged 75 years or more on January 1, 1995, regardless of whether the co-twin was alive. The first wave included 3,099 individuals. Face-to-face interviews were completed by 100 interviewers during a 3-month period (February–April 1995). A total of 2,401 interviews were conducted, corresponding to a participation rate of 77 percent. Two years later, the survey was repeated among survivors from the 1995 wave, as well as an additional 779 twins aged 73–76 years. The overall response rate in the 1997 wave of the LSADT (LSADT-97) was 79 percent. In 1999, all surviving 1997 participants were recontacted, and all twins who in the meantime had turned 70 years or more were included in the study population. The third wave of the LSADT (LSADT-99) had an overall participation rate of 70 percent. Mortality follow-up for all participants was conducted through register linkage with the Civil Registration System.

An intrinsic problem in studies of functional and cognitive disabilities among the elderly is that persons with more severe disabilities may not be able to participate in the study interview. Therefore, in this study, proxy interviews were sought when the twin was unable to participate. The fraction of proxy interviews was less than 10 percent in all three surveys.

Of the 2,401 participants in LSADT-95, 421 (18 percent) died before LSADT-97, and 385 (16 percent) refused participation in LSADT-97; this resulted in 1,595 reinterviews. This meant that 81 percent of the surviving 1995 participants were reinterviewed in 1997. Of the 1,595 two-wave participants, 265 (17 percent) died before LSADT-99 and 346 (22 percent) were nonresponders. Thus, 984 individuals participated in all three waves of the study, corresponding to a reinterview rate of 74 percent for the surviving participants from the first two waves (figure 1). These 984 individuals included 133 intact twin pairs and 718 twins who had a deceased or nonparticipating co-twin.

The 2,401 participants in LSADT-95 included a large number of twins whose co-twin had died prior to the survey. Thus, LSADT-95 included only 480 intact twin pairs, 475 of which were same-sex pairs of known zygosity. In 451 of these 475 same-sex twin pairs, both members of the pair completed the 1995 functional ability assessment (54 monozygotic male pairs, 128 monozygotic female pairs, 79 dizygotic male pairs, and 190 dizygotic female pairs). The number of intact twin pairs completing the functional ability assessment dropped to 247 in 1997 (31 monozygotic male pairs, 74 monozygotic female pairs, 38 dizygotic male pairs, and 104 dizygotic female pairs) and 127 in 1999 (17 monozygotic male pairs, 45 monozygotic female pairs, 20 dizygotic male pairs, and 45 dizygotic female pairs).

Functional abilities

In this study, we used an instrument (Avlund) that has previously been validated in Denmark (10, 22, 23). Assessment of functional abilities was based on self-report,

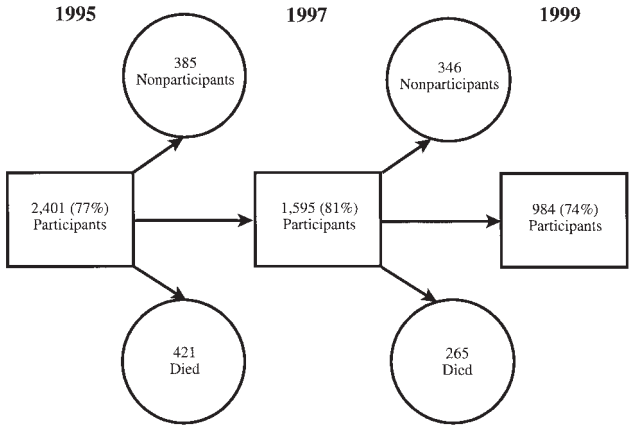

FIGURE 1. Pattern of participation in the Longitudinal Study of Aging Danish Twins, 1995–1999. At intake in 1995, the study population comprised 3,099 Danish twins aged 75 years or more (with or without a living co-twin) who were registered in the population-based Danish Twin Registry. Face-to-face interviews were completed with 2,401 (77%).

which has generally been found to be reliable and valid (24, 25). The Avlund instrument has been described in detail previously, and it has been shown to discriminate between levels of functional ability among community-dwelling elderly persons through questions about tiredness and the need for personal assistance in relation to functional abilities (22, 23). The Avlund instrument was extended to include assessment of the need for medical equipment or aids in relation to functional abilities, based on results showing that equipment and aids can improve functional abilities among the elderly (26). All of the items from the Katz index of Activities of Daily Living were included (27), as well as questions about the ability to see and hear and the ability to engage in more demanding activities such as running (10).

For identification of meaningful quantitative subscales, the 26 items were factor-analyzed in the total LSADT-95 twin sample. All functional ability items were rated on a scale of 1 to 4, with the following response options: 4 = can do without fatigue; 3 = can do with fatigue or minor difficulties; 2 = can do with an aid or with major difficulties; and 1 = cannot do. In the factor analyses, three factors had an eigenvalue of more than 1, but few of the items loaded on the third factor. Therefore, a two-factor solution was adopted. The first factor loaded highest on items dealing with the ability to walk, run, climb stairs, and carry weights and was interpreted to reflect a dimension of strength. The second factor loaded highest on items dealing with the ability to dress and wash oneself and get into and out of bed; this factor was interpreted to reflect a dimension of agility.

Scores for the two dimensions were calculated by taking the average response of items that loaded highest on the factor or had been judged to be relevant for that dimension. The internal consistency reliability estimate for the strength scale was 0.93 in both the male and female samples for both the in-person interviews and the proxy interviews. The reliability estimates for the agility scale were also the same for

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men and women and equaled 0.91 for the in-person interview and 0.93 for the proxy interview. These values indicate very reliable scales. The correlation between the strength scale and the agility scale was 0.77. The later surveys yielded very similar results.

In this study, we focused on the strength scale, since the small variability in the agility scale led to its being dropped from the assessment in 1999. Rate of change for an individual was measured as the regression slope of the three strength scores on time of assessment separately for each individual. Because the three assessments were equally spaced 2 years apart, the slope is mathematically equivalent to the difference between the 1999 and 1995 scores.

Analysis of twin similarity

Classical analyses. In humans, two types of twinning occur: monozygotic and dizygotic. Monozygotic (identical) twins share all of their genetic material, and dizygotic (fraternal) twins, like ordinary siblings, share, on average, 50 percent of their genes (i.e., 50 percent of their genes are identical by descent). In the classical twin study, monozygotic and dizygotic intraclass correlations for a given trait are compared. A significantly higher correlation in monozygotic twins indicates that genetic factors play an etiologic role.

To estimate the heritability of the functional ability scales (i.e., the proportion of the population variance attributable to genetic variation) in this study, we analyzed the twin data using standard biometric models (28). In such a case, the total variance (V) in a scale is decomposed as $V = A + D + C + E$, where A refers to the variance contribution of additive genetic effects, D refers to the variance contribution of genetic effects due to dominance (intralocus interaction), C refers to the variance contribution of shared environmental effects (i.e., environmental factors that are shared by twins reared together and are thus a source of their similarity), and E refers to the variance contribution of nonshared environmental effects (i.e., environmental factors that are not shared by twins reared together and are thus a source of their dissimilarity). Assuming that shared environmental effects contribute equally to the resemblance of monozygotic (MZ) and dizygotic (DZ) twins, the expected twin covariances under this model are given by $\mathrm{Cov(MZ)} = A + D + C$ and $\mathrm{Cov(DZ)} = (½)A + (¼)D + C$. Previous analysis of the 1995 data indicated that the functional ability data could be fitted adequately with a model that included only additive genetic (A) and nonshared environmental effects (E) that varied in magnitude in the male and female subsamples (10). Consequently, in the current analysis, only AE models were fitted to the twin data separately in the male and female subsamples. Prior to model-fitting analysis, the observed twin variances and covariances were stratified by sex. For correction of unequal variances between twin 1 and twin 2 in the smaller subgroups, the data were double-entered, and the degrees of freedom were adjusted accordingly.

Growth model. For assessment of the contribution of genetic factors to functional ability at each of the individual assessments as well as rate of change in functional ability across assessments, a "growth" model was fitted to the observed twin data (29). The model we fitted is depicted in figure 2 at the phenotypic level. Specifically, variation at each assessment was decomposed into the contribution of up to three factors: a level effect (equivalent to the average functional ability across assessments), a slope effect (equivalent to the difference in functional ability between the last and first assessments), and a residual effect.

The model in figure 2 was applied to the twin data assuming the biometric decomposition given above for each of the phenotypic factors (e.g., level, slope). Again only AE models were fitted to the twin data, with models being fitted separately in the male and female samples. Biometric models were fitted to the twin data using the maximum likelihood procedure implemented in the Mx software package (30). To account for attrition effects, twins lost to follow-up were treated as missing in the specification of the likelihood. Thus, observations lost to follow-up was treated as missing at random in the analysis (31). Prior to model-fitting, twin means, variances, and correlations for the various phenotypes were estimated using the same likelihood procedure. Likelihood-based 95 percent confidence interval estimates of parameters were computed using the procedures described by Neale and Miller (32).

RESULTS

Among the 984 individuals participating in all three assessments, 966 (98 percent) had a valid strength score from all three waves. This left 127 intact twin pairs (62 monozygotic pairs and 65 dizygotic pairs) for rate-of-change twin analyses.

Table 1 documents that even at the single-item level, functional abilities showed a systematic decline in mean score over time accompanied by a high within-person corre-

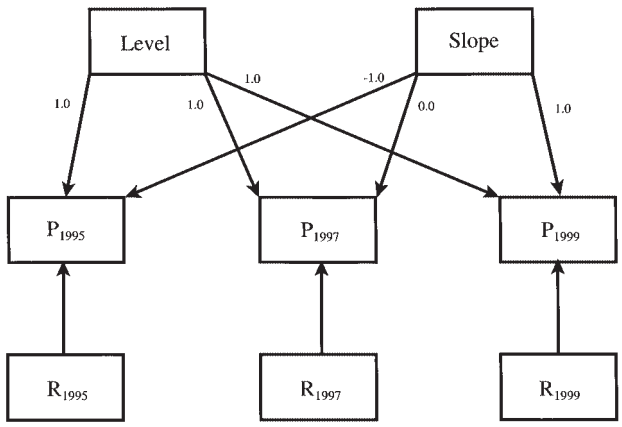

FIGURE 2. "Growth" model that was the basis of a biometric analysis of longitudinal data on functional abilities, Longitudinal Study of Aging Danish Twins, 1995–1997. The model includes phenotypes (P) that are functional ability scores at each wave of assessment (1995, 1997, and 1999). These scores are represented as being the result of three factors: a level effect (which was parameterized as the average score over assessments), a slope effect (which is equivalent to the difference between the last and first assessments), and a residual (R) (which reflects deviations from linearity).

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TABLE 1. Functional ability scores for 966 individuals participating in three waves of the Longitudinal Study of Aging Danish Twins, 1995–1999

Functional ability	Mean score*						Within-person correlation in score		
	1995		1997		1999		1995–1997	1995–1999	1997–1999
	Mean	SD†	Mean	SD	Mean	SD			
Walk around in the house	3.76	0.65	3.68	0.74	3.49	0.93	0.63	0.55	0.67
Walk up and down stairs one floor	3.58	0.85	3.84	1.00	3.12	1.16	0.67	0.59	0.68
Walk up stairs to the second floor	3.34	1.03	3.05	1.16	2.80	1.26	0.64	0.55	0.64
Get outdoors	3.57	0.84	3.41	0.95	3.17	1.09	0.60	0.54	0.62
Walk 400 m without resting	3.58	0.90	3.33	1.11	3.02	1.27	0.63	0.52	0.63
Do light exercise	3.13	1.21	2.82	1.32	2.69	1.36	0.51	0.46	0.56
Do hard exercise	1.78	1.15	1.67	1.12	1.54	1.03	0.41	0.38	0.40
Walk in nice weather for ½–1 hour	3.11	1.10	2.99	1.24	2.81	1.29	0.63	0.57	0.63
Walk in bad weather for ½–1 hour	3.10	1.25	2.70	1.35	2.48	1.38	0.62	0.54	0.62
Run 100 m	2.04	1.29	1.70	1.14	1.12	0.58	0.62	0.42	0.53
Carry 5 kg	3.29	1.11	2.98	1.26	2.78	1.32	0.61	0.55	0.66
Strength score (mean of above 11 items)	3.14	0.79	2.89	0.86	2.65	0.91	0.79	0.73	0.82

* For each item and for the summary strength score, the maximum score was 4.0, corresponding to being able to do the activity without any limitation; the minimum score was 1.0, corresponding to not being able to perform the activity at all.
† SD, standard deviation.

lation. As expected, this pattern is even more clear for the summary strength score, which showed a decline of one quarter to one third of a standard deviation for every 2-year period and a within-person correlation of approximately 0.8 for both the 2-year interval and the 4-year interval. A similar pattern was found for all of the age and sex groups shown in table 2.

On the basis of the sign of the regression slope, it was found that 76.5 percent of the 966 participants declined in strength score, while 9.8 percent had no change and 7.9 percent improved their performance. The regression slope did not correlate with sex ($r = -0.07$, not significant), and it correlated only to a small degree with age at intake ($r = 0.14$, $p < 0.05$).

Table 3 shows the strength scores stratified for participation in the follow-up studies. The twins who died between two interview waves had, in their last assessment, an average strength score approximately one standard deviation below that of the individuals who did not die between two waves. Furthermore, twins who died between 1997 and 1999 showed a greater decline between 1995 and 1997 than twins who survived, which is consistent with a pattern of terminal decline. Alternatively, the surviving nonparticipants, in their last assessment, had scores only slightly lower than those of the individuals who participated in the next wave.

Table 4 gives mean values and correlations for the four sex/zygosity twin-pair samples at each assessment. All four twin groups showed mean-level performance declines of approximately one third of a standard deviation for each 2-year retest interval. There was also consistent evidence for a modest increase in variance over time. The twin correlations

TABLE 2. Strength scores for 966 individuals participating in three waves of the Longitudinal Study of Aging Danish Twins, 1995–1999

Sex and age group (years) in 1995	No. of participants	Mean strength score*						Within-person correlation in score		
		1995		1997		1999		1995–1997	1995–1999	1997–1999
		Mean	SD†	Mean	SD	Mean	SD			
Males										
75–79	166	3.49	0.57	3.27	0.78	2.99	0.85	0.77	0.64	0.74
80–84	117	3.25	0.80	3.00	0.89	2.72	0.92	0.80	0.75	0.86
85–89	51	2.82	0.84	2.66	0.89	2.23	0.90	0.85	0.63	0.74
≥90	5	2.52	0.98	2.30	0.98	1.96	0.84			
Females										
75–79	313	3.28	0.71	3.06	0.79	2.88	0.82	0.77	0.74	0.83
80–84	198	2.90	0.79	2.69	0.79	2.46	0.87	0.73	0.67	0.79
85–89	100	2.66	0.83	2.29	0.82	2.07	0.82	0.76	0.68	0.77
≥90	16	2.64	0.70	2.23	0.73	1.29	0.72	0.82	0.73	0.66

* For each item and for the summary strength score, the maximum score was 4.0, corresponding to being able to do the activity without any limitation; the minimum score was 1.0, corresponding to not being able to perform the activity at all.
† SD, standard deviation.

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TABLE 3. Strength scores for participants in the Longitudinal Study of Aging Danish Twins, according to participation in follow-up studies in 1997 and 1999, 1995–1999*

Status and reason for nonparticipation	Mean age (years) in 1995		% of females	Mean strength score†					
				1995		1997		1999	
	Mean or no.	SD‡		Mean or no.	SD	Mean or no.	SD	Mean or no.	SD
Participated in all three waves									
Age	80.3	4.2	65	3.13	0.79	2.88	0.86	2.65	0.91
No. of subjects	984			983		983		968	
Dropped out between 1997 and 1999									
Died									
Age	82.9	5.0	60	2.52	0.92	1.95	0.85		
No. of subjects	265			264		263			
Refused									
Age	81.0	4.6	69	2.82	0.89	2.56	0.95		
No. of subjects	346			344		346			
Dropped out between 1995 and 1997									
Died									
Age	83.6	5.3	56	2.04	0.94				
No. of subjects	421			415					
Refused									
Age	81.4	4.6	69	2.78	0.90				
No. of subjects	385			378					

* A total of 966 persons had a valid score from all three waves. Available data for all 984 participants are included in the table.
† For each item and for the summary strength score, the maximum score was 4.0, corresponding to being able to do the activity without any limitation; the minimum score was 1.0, corresponding to not being able to perform the activity at all.
‡ SD, standard deviation.

were generally consistent across assessment points. In the male sample, there was very little evidence for twin similarity, since none of the estimated correlations were statistically significant (as judged by the width of the corresponding 95 percent confidence intervals) and the monozygotic and dizygotic correlations were generally similar; this suggests minimal genetic effects. In contrast, for the female sample, the monozygotic correlation exceeded the dizygotic correlation at each assessment, and both correlations were statistically significant. In each of the three assessments (1995, 1997, and 1999), the female monozygotic correlation was in the range of 0.40–0.42, while the corresponding range for the female dizygotic correlation was 0.22–0.27; this suggests moderate genetic effects. The male participant sample in our study was small because of the poorer survival rate of men relative to women, not because of differences in participation rates. Although heritability estimates were uniformly low in the male participant sample, the size of the sample was not sufficiently large to allow for precise estimates of heritability, as is reflected in the large confidence intervals.

Also shown in table 4 are the estimated twin correlations for the level and slope parameters. The level correlations are comparable to the correlations observed at the individual assessments, which suggests that aggregating across assessments had little impact on twin similarity. Thus, correlations were low, were not statistically significant, and differed minimally between monozygotic and dizygotic twins in the male sample; but correlations were moderate, were statistically significant, and showed the expected monozygotic-dizygotic difference in the female sample. Correlations for the slope parameter also evidenced the same pattern of male-female difference, although the slope correlations were overall much lower than the level correlations. This suggests that if there are genetic influences on rate of change in functional ability, the magnitude of those influences is much smaller than that for overall level.

The results of fitting the growth model to the twin data are summarized in table 5 in terms of the estimates of heritability (with associated confidence intervals). Because there was a significant difference in parameter estimates in the male and female samples ($\chi^2 = 27.9$, 12 df; $p = 0.006$), estimates are given separately for men and women. Heritability estimates were uniformly low and nonsignificant in the male sample. In the female sample, heritability was 43–44 percent for individual assessments and 48 percent for the level parameter. However, estimated heritability for the slope parameter was statistically nonsignificant in both the female sample and the male sample.

DISCUSSION

Using a population cohort of Danish twins initially aged ≥75 years who were assessed in three waves over a 4-year period, we found little evidence for heritable effects on rate of change in functional abilities. In men, the proportion of

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TABLE 4. Strength scores* and twin intraclass correlations for strength scores among twin pairs participating in the Longitudinal Study of Aging Danish Twins, 1995–1999

	1995					1997					1999					All three study waves				
	No. of pairs	Mean score	SD†	Intraclass correlation	95% CI†	No. of pairs	Mean score	SD	Intraclass correlation	95% CI	No. of pairs	Mean score	SD	Intraclass correlation	95% CI	No. of pairs	Level correlation‡,§	95% CI	Slope correlation‡,¶	95% CI
Males																				
MZ†	54	3.2	0.77	−0.02	−0.28, 0.24	31	2.8	1.0	0.07	−0.25, 0.37	17	2.7	1.0	0.22	−0.18, 0.59	17	0.12	−0.19, 0.41	−0.10	−0.57, 0.42
DZ†	79	3.0	0.89	0.01	−0.21, 0.23	38	2.7	0.98	0.11	−0.15, 0.35	20	2.4	1.0	0.03	−0.28, 0.34	20	0.06	−0.19, 0.30	−0.06	−0.40, 0.30
Females																				
MZ	128	3.0	0.88	0.42	0.27, 0.55	74	2.7	0.89	0.40	0.22, 0.55	45	2.5	0.92	0.40	0.20, 0.58	45	0.44	0.27, 0.58	0.27	0.002, 0.50
DZ	190	2.8	0.89	0.22	0.08, 0.35	104	2.6	0.92	0.24	0.08, 0.38	45	2.4	0.96	0.27	0.10, 0.43	45	0.29	0.15, 0.43	−0.05	−0.27, 0.18

* For the summary strength score, the maximum score was 4.0, corresponding to being able to do activities without any limitation; the minimum score was 1.0, corresponding to not being able to perform activities at all.
† SD, standard deviation; CI, confidence interval; MZ, monozygotic; DZ, dizygotic.
‡ Intraclass correlation.
§ Sum of strength scores in 1995, 1997, and 1999.
¶ Calculated as the regression slope based on strength scores in 1995, 1997, and 1999.

variance in the rate-of-change measure that was associated with genetic factors (i.e., heritability) was only 9 percent; the comparable value in the female sample was only 16 percent. Neither heritability estimate was statistically significant. The failure to find heritable influences on our measure of rate of change in functional abilities was unexpected, given that the measure did reliably assess rate of change in functional abilities at the individual level and was moderately heritable (at least in the female sample) at each individual wave of assessment.

Twin studies in the very old can be influenced by selective survival. Functional abilities are correlated with survival; furthermore, the survival of twins is correlated, which can produce spurious results (33). However, the correlation in life-span for twins is modest (about 0.25 for monozygotic twins and about 0.05 for dizygotic twins (7)). As expected, the twins who died between two waves had a lower average strength score at their last assessment than the twins who participated in the subsequent wave (see table 3). It was reassuring, however, that the surviving nonparticipants ("refusers") were quite similar to the twins who stayed in the study, which suggests that there was no substantial selective nonparticipation among the survivors. In any case, all twin pairs who completed the initial assessment were included in the biometric analysis of the longitudinal data, so selective survival is not a likely explanation for our failure to observe heritable influences on rate of change in functional abilities.

Functional abilities among the elderly can be conceptualized as being determined by both a "starting level" and rate of change, and genetic influences on both might be expected. Several cross-sectional studies in the elderly have demonstrated substantial genetic influences on physical and cognitive functioning over a broad range of phenotypes. However, there have been few published studies on the heritability of rate-of-change traits. A longitudinal analysis of middle-aged female twins over a 10-year interval found substantial heritability for changes in body mass index and moderate heritability for changes in coronary heart disease risk factors (14, 15). Studies of male twins have also indi-

TABLE 5. Heritability analysis of strength scores* in the Longitudinal Study of Aging Danish Twins, 1995–1999

	Males		Females	
	h^2†	95% CI‡	h^2†	95% CI
Strength score				
1995	0.05	0.00, 0.26	0.43	0.30, 0.54
1997	0.13	0.00, 0.38	0.43	0.28, 0.59
1999	0.15	0.00, 0.50	0.44	0.28, 0.57
Level§	0.12	0.00, 0.39	0.48	0.34, 0.59
Slope¶	0.09	0.00, 0.44	0.16	0.00, 0.35

* For the summary strength score, the maximum score was 4.0, corresponding to being able to do activities without any limitation; the minimum score was 1.0, corresponding to not being able to perform activities at all.
† Heritability under a genetic model including additive genetic factors and nonshared environment.
‡ CI, confidence interval.
§ Sum of strength scores in 1995, 1997, and 1999.
¶ Calculated as the regression slope based on strength scores in 1995, 1997, and 1999.

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cated a genetic influence on change in weight over a 43-year interval (13) but not on bone loss over a 16-year interval (12). A common feature of all of these studies is that the heritability of rate of change is not larger than the heritability of the phenotypes in cross-sectional analyses.

It has recently been suggested that rate-of-change phenotypes may be especially appropriate targets for molecular genetic investigations aimed at identifying the specific genes influencing human aging (11). This recommendation does not appear to have received support in previous investigations of rate-of-change phenotypes that have reported relatively low levels of heritability (12–15). To be successful, a large-scale molecular genetic study of a rate-of-change phenotype should, at a minimum, satisfy the following criteria: 1) rate of change is inexpensively and reliably assessed; 2) attrition over the multiple waves of assessment is minimal; and 3) rate of change is at least moderately heritable.

Our analysis of the strength measure illustrates some of the difficulties geneticists will have in attempting to identify suitable rate-of-change phenotypes for molecular genetic investigation. There is, of course, overwhelming evidence that functional ability declines with age, and our analysis of the strength measure confirmed that decline over a 4-year period in a sample of persons who were 80 years old, on average, at initial assessment. Importantly, decline in strength scores was observed at the individual level as well as the aggregate level. Nearly 80 percent of the sample of individuals who participated in all three waves of assessment showed a negative slope of strength score against assessment wave. The costs associated with administering the strength scale are relatively low, yet the resulting scale has impressive reliability and validity properties. Item-level responses paralleled the decline observed at the aggregate level, and a very high intercorrelation of responses over assessments was observed at the scale level as well as at the individual item level.

Nonetheless, it would be difficult to argue that rate of change on the strength scale would be a suitable phenotype for molecular genetic investigation. Biometric analysis of the twin data indicated that the heritability of rate of change on the strength scale was modest and not statistically significant in both the male and female samples. It may be that retest intervals longer than 4 years would produce rate-of-change phenotypes that were more heritable than was observed in the 4-year interval used in the present study. For example, Fabsitz et al. (13) reported that change in body mass index over a 43-year interval was 70 percent heritable in a sample of men aged 23 years (on average) at initial assessment. Identifying heritable influences on rate-of-change phenotypes may require initial samples of persons who are middle-aged or younger at initial assessment, with retest intervals that are measured in decades rather than single years. However, molecular geneticists are not likely to want to wait 40, 20, or even 10 years to obtain material for their investigations, and long retest intervals are likely to be associated with relatively high levels of attrition (loss to mortality was a major factor in our sample of predominantly octogenarians). Nonetheless, follow-up of large middle-aged samples originally assessed many years previously may be an attractive alternative to trying to measure rate of change in an elderly sample.

Experience with the LSADT provides further evidence of the difficulty of assessing rate of change in elderly samples for molecular genetic investigation. In the LSADT, participation rates at each wave of assessment were relatively high, probably because the assessment was relatively brief (less than 2 hours) and was completed in the respondent's residence. Nonetheless, 60 percent of the sample members who completed the 1995 survey did not participate in the 1999 survey, half being lost to mortality. Sample loss was even more pronounced at the twin-pair level, since only 127 (28 percent) of the 451 pairs who completed the strength assessment in 1995 completed it again in 1999. Thus, researchers conducting candidate gene studies of rate-of-change phenotypes (which would be based on samples of individuals) might expect that 60 percent or more of a sample of very old persons would be lost to follow-up, while in genetic linkage studies of rate of change (which would be based on samples of relatives), there might be a sample loss to follow-up as high as 70 percent. Clearly, attrition rates like these represent a significant challenge to large-scale molecular genetic studies of rate-of-change phenotypes, even when they are based on long retest intervals.

Our analysis of the strength scale at the individual waves of assessment suggests an alternative approach for identifying phenotypes for molecular genetic analysis in human aging research. At each wave of assessment, strength scores were moderately heritable, at least in the female sample, and aggregating scale scores over multiple waves of assessment had little impact on heritability. This suggests that a single assessment would suffice in identifying all of the relevant genetic variance. We believe that the strength score in this sample of very old persons probably does reflect rate of change, albeit over a very long interval. Even though our sample was not assessed earlier in life, we can confidently say that the vast majority of LSADT participants were able to walk up two flights of stairs, engage in light exercise, and run 100 m when they were young and middle-aged. The difficulties they are having with these activities in late life thus reflect a change from a higher level of functioning. Consequently, a single-wave assessment of physical functioning might be an attractive alternative to assessing rate of change over multiple waves of assessment.

Understanding the genetic contribution to human aging should be a priority in gerontologic research over the next decade. Nonetheless, our analysis of the multiple waves of functional ability data in the LSADT serves to highlight some of the difficulties human molecular geneticists will encounter as they turn their attention to aging. At this initial stage of inquiry, it is essential that a range of phenotypes and research designs be critically evaluated for their suitability to support molecular genetic analysis.

ACKNOWLEDGMENTS

This study was supported by the US National Institute on Aging (grant NIA-PO1-AG08761), the Danish Research Councils, and the Danish National Research Foundation.

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